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Abstract: This retrospective single-center study investigated the incidence of neurologic injury as determined by autopsy or cerebral imaging in 74 patients undergoing extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome. Seventy-three percent of patients were treated with venovenous and 27% with venoarterial ECMO. ECMO-associated intracerebral hemorrhage was diagnosed in 10.8% of patients. There were no cases of ischemic stroke. Clinical characteristics did not differ between patients with and without neurologic injury. Six-month survival was 13% (Wilson confidence interval, 2%-47%) in patients with severe intracerebral hemorrhage compared to an overall survival rate of 57% (Wilson confidence interval, 45%-67%).

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Neurologic Injury With Severe Adult Respiratory Distress Syndrome in Patients Undergoing Extracorporeal Membrane Oxygenation: A Single-Center Retrospective Analysis

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This retrospective single-center study investigated the incidence of neurologic injury as determined by autopsy or cerebral imaging in 74 patients undergoing extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome. Seventy-three percent of patients were treated with venovenous and 27% with venoarterial ECMO. ECMO-associated intracerebral hemorrhage was diagnosed in 10.8% of patients. There were no cases of ischemic stroke. Clinical characteristics did not differ between patients with and without neurologic injury. Six-month survival was 13% (Wilson confidence interval, 2%–47%) in patients with severe intracerebral hemorrhage compared to an overall survival rate of 57% (Wilson confidence interval, 45%–67%). (Anesth Analg 2017;125:1544–8)

Extracorporeal membrane oxygenation (ECMO) is increasingly used in cases of respiratory or circulatory failure refractory to conventional treatment. Neurologic injury, including cerebrovascular hemorrhage, ischemia, and infarction, is a complication of ECMO linked to increased morbidity and mortality. Most data on neurologic injury derive from patients undergoing ECMO for cardiac indications or after cardiopulmonary resuscitation[1] with additional smaller data sets in patients treated with either venovenous (v-v) or venoarterial (v-a) ECMO for other cardiac and respiratory indications.[2,3] As a result, the reported rate of neurologic injury ranges widely from 11% to 50%. In a 2009 patient cohort receiving mainly v-v ECMO for H1N1 influenza–associated acute respiratory distress syndrome (ARDS), the rate of intracerebral hemorrhage (ICH) was 9%[4] and 11% in patients undergoing v-v ECMO for other indications.[5] The aim of this single-center report was to describe the incidence of neurologic injury in patients undergoing ECMO for severe ARDS and briefly review existing literature.

METHODS

Ethical Approval and Consent to Participate

This retrospective analysis was approved by the Cantonal Ethikkommission Zurich (KEK-ZH-Nr. 2014-0318), which waived the need for informed consent.

Study Design and Objectives

All patients undergoing ECMO therapy for ARDS at the University Hospital of Zurich between January 1, 2008, and December 31, 2013, were included. Local guidelines were used as criteria for initiating ECMO as previously described.[6] ECMO was performed primarily in the v-v configuration. V-A cannulation was chosen in selected patients when v-v ECMO was anticipated to be insufficient, as in cases of moderate to severe heart failure, severe hypoxemia, hemodynamic instability, or pulmonary hypertension.

While on ECMO, the hematocrit was maintained above 28% and platelet count was kept over 50,000/μL. Unfractionated heparin was administered to target an antifactor Xa activity of 0.2–0.3 IU/mL or activated clotting time (ACT) of 150–180 seconds for all ECMO.

Data Collection

Baseline values were collected on all patients. During ECMO therapy, the lowest thrombocyte count, lowest hematocrit, and highest antifactor Xa activity and ACT value were recorded, as was survival 6 months after ECMO initiation. Patient charts were reviewed for clinical evidence of neurologic dysfunction during ECMO treatment, defined as seizures, loss of consciousness, and loss of brainstem reflexes or new-onset anisocoria. All cerebral imaging studies were reviewed by S.K. and U.S.

In accordance with Swiss law, autopsies were only performed when the next of kin rendered approval. Available autopsy records and slides were reviewed by E.J.R. If the macroscopic autopsy examination showed only evidence of diffuse hypoxic-ischemic changes, a follow-up histologic examination was not routinely performed. The cerebral imaging or autopsy findings were classified as either probably related to or unlikely due to ECMO therapy by U.S. and E.J.R., who were blinded to each other's assessment. Because no known pathognomonic morphologic or imaging findings for ECMO-associated neurologic injury exist, the classification was based on the features of the acute illness, localization, and the neuropathologic findings. More

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specifically, the presence of hemorrhagic and/or ischemic lesions not attributable to the underlying disease was considered related to ECMO therapy.

Statistical Analysis

The primary outcome of the study was the incidence of neurologic injury on ECMO, while survival, baseline values, intensive care unit, and ECMO characteristics were secondary outcome parameters. Continuous variables of baseline-, intensive care unit–, and ECMO-specific parameters were compared between patients with and without neurologic injury using the Mann-Whitney *U* test. Categorical variables were compared using Pearson χ^2 test or Fisher exact test, as appropriate. All *P* values were 2 sided and considered statistically significant if $P \leq .05$.

Due to the retrospective nature of the study, the number of patients available was given. Assuming an overall survival of 62%, a survival of injured patients of 20%, and a proportion of injured patients of 11%, the survival of noninjured patients would be 67%. Based on 74 patients, and a significance level of 5%, the Fisher exact test was calculated to have a power of 65%.

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY).

RESULTS

During the study period of 6 years, a total of 309 ECMO runs were performed at our institution. Of these, 74 patients suffering from severe ARDS received ECMO therapy. Forty-two patients (57%) survived to 6 months after ECMO initiation (Wilson confidence interval, 45%–67%).

Cerebral imaging was performed in 20 patients. Due to unsatisfactory quality, 1 imaging study was not eligible for investigational purposes. Nineteen patients underwent computed tomography evaluation, and 1 patient underwent magnetic resonance tomography. An autopsy was performed in 18 patients. In 1 patient, the autopsy did not include the brain.

Cerebral imaging and/or autopsy was thus performed in 23 of 32 nonsurvivors (72%), while cerebral imaging was performed in 8 of 42 survivors (19%).

Evidence of presumed ECMO-associated neurologic injury was diagnosed by cerebral imaging and/or autopsy in 8 patients (10.8%). In all cases, ICH with variable localization and dimensions were diagnosed (Table and Figure). There were no cases of ischemic stroke.

In 3 patients, neurologic injury was assessed as not being associated with ECMO therapy. Two patients with sepsis had large intraparenchymal hemorrhagic lesions, which were considered likely due to septic-embolic origin. A single patient diagnosed with posterior reversible leukoencephalopathy syndrome in the clinical setting of preeclampsia had multiple, bihemispheric ischemic cerebral infarcts with hemorrhagic transformation.

Patients with and without neurologic injury did not differ in baseline characteristics and coagulation parameters. Patients with and without neurologic injury were comparable with respect to age (median, 45 [interquartile range {IQR}, 29–60] vs 49 [36–58]; $P = .8$), sex (n = 6 [75%] vs 36 [55%]; $P = .5$), and Simplified Acute Physiology Score (median, 47 [IQR, 37–55] vs 52 [34–64]; $P = .5$). No difference between groups in hematologic parameters (minimal thrombocyte count: median, 68 G/L [IQR, 36–134] vs 49 G/L [25–102]; $P = .5$ and minimal hematocrit: median, 22% [IQR, 21–27] vs 21% [19–24]; $P = .6$) and anticoagulation values (maximal antifactor Xa activity of unfractionated heparin: median, 0.72 IU/mL [IQR, 0.38–0.76] vs 0.64 IU/mL [0.42–1.0]; $P = .7$ and maximal ACT: median, 218 seconds [192–239] vs 225 seconds [207–264]; $P = .2$) were observed.

In patients with neurologic injury, 1 patient (13%) received v-a cannulation compared to 19 patients (29%) without neurologic injury. The rate of neurologic injury did not differ between v-a and v-v cannulation mode ($P = .4$, Fisher exact test).

Seven of 8 patients with ECMO-associated neurologic injury died, yielding a survival rate of 13%. Therapy was withdrawn in 5 patients due to severe neurologic injury and complete dependence on ECMO support. Two patients died due to complications: hemorrhagic shock after accidental dislocation of the ECMO cannula and circulatory failure due to pericardial tamponade.

The diagnosis of ECMO-associated neurologic injury was made at a median of 6 days (IQR, 4–23 days) after ECMO initiation. Patients with ECMO-associated neurologic injury died at a median of 14 days (IQR, 6–31 days) after ECMO initiation.

DISCUSSION

In our cohort of 74 patients requiring ECMO for ARDS, ECMO-associated intracranial hemorrhage was diagnosed in 10.8% of patients with a 6-month survival of 13% (Wilson confidence interval, 2%–47%) compared to 57% overall (Wilson confidence interval, 45%–67%). Although direct comparison of our results with those found in other studies is difficult due to diverse study populations, methods, and the definition of neurologic injury, our data are consistent with previously reported incidences ranging from 3% to 19%.[2,4,5,7–9] We were unable to identify a precise trigger for this devastating event in our cohort. Logistical challenges that precluded neuroimaging studies in all ECMO patients may have resulted in an underestimation of the true incidence of neurologic injury in our study. In contrast to the 2% reported by Luyt et al,[5] ischemic stroke was not diagnosed in our study population.

The impact of ICH on patient outcome in our report is also consistent with published mortality rates of 60%–92%.[2,7,9] The principal finding in our study on cerebral imaging and autopsy was major ICH with fatal outcome, while small ICH was diagnosed only in a minority of patients. This observation emphasizes the high probability for underdiagnosis of neurologic injury in minor events. Hematomas diagnosed at autopsy were smaller than the large space-occupying, intraparenchymal hematomas seen in patients where therapy was withdrawn. As reported by Risnes et al,[3] this observation suggests that the true incidence of neurologic injury was higher in both survivors and nonsurvivors. It is possible that impaired coagulation gradually increases hemorrhage in patients undergoing ECMO therapy with anticoagulation, possibly representing a plausible explanation for the late onset of clinical signs.

Table. Pathologic Finding on Cerebral Imaging and/or Autopsy—Detailed Description

				Cerebral Imaging			Autopsy		
Sex, Age	Acute Disease[a]/Additional Disease[b]	Cannulation	Clinical Finding	Diagnosis	Modality	ECMO Association	Diagnosis	ECMO Association	Survival, 6 mo
M, 67	Pneumonia/none	v-v	2,4	**Multiple bihemispheric intraparenchymal hemorrhages parietal and basal nuclei with rupture into the ventricle**. Edema	CT	Yes	**Bihemispheric intraparenchymal and subarachnoidal hemorrhage**	Yes	No
M, 42	Mediastinitis/none	v-a	3,4	**Massive parietal intraparenchymal hemorrhage with rupture into the ventricle**, edema, uncal herniation	CT	Yes	-	-	No
F, 17	Pneumonia/thalassemia	v-v	3,4	**Bihemispheric intraparenchymal hemorrhage**, global vasogenic edema, transforaminal herniation	CT	Yes	-	-	No
M, 47	Necrotizing fasciitis/none	v-v	…	**Small frontal subarachnoid hemorrhage**	CT	Yes	-	-	Yes
M, 59	Pneumonia/Waldenström macroglobinemia	v-v	4	Ischemic infarction—right anterior and middle cerebral artery. **Intraparenchymal hemorrhage frontal left**. Edema. Uncal herniation	CT	Yes	Infarction A. cerebri anterior and media right with midline shift. **Intraparenchymal and subarachmoidal hemorrhage frontal left**	Yes	No
M, 20	Drowning/none	v-a	3, 4	**Intraparenchymal right-sided hemorrhage basal ganglia, mesencephalon, and pons**. Occlusive hydrocephalus, generalized edema, transforaminal herniation	CT	Yes	**Massive right intraparenchymal hemorrhage extending to the brainstem, rupture into the ventricle.** Severe edema. Hypoxic brain injury	Yes	No
M, 61	Pneumonia/none	v-v	-	-	…	-	**Petechial brainstem hemorrhages**	Yes	No
F, 38	Influenza/none	v-v	-	-	…	-	**Multiple bihemispheric and cerebellar hemorrhages**	Yes	No
F, 34	Preeclampsia with extensive PRES/none	v-a	4	Multiple bihemispheric ischemic infarcts temporal and frontobasal with hemorrhagic transformation	MRT	No	-	-	Yes
F, 49	Septic shock/none	v-a	4	No pathologic findings	CT	No	Multiple intraparenchymal purpura-like hemorrhage due to septic emboli	No	No
F, 56	Septic shock/none	v-a	1, 2, 3, 4	Multiple bihemispheric hypodense lesions corresponding to septic emboli with small microbleeds. Global edema, transforaminal herniation	CT	No	-	-	No

Findings on cerebral imaging or in autopsy probably associated with ECMO therapy in bold type. Dash indicates that imaging or autopsy was not performed.

Abbreviations: Clinical Finding 1, seizures; Clinical Finding 2, loss of consciousness; Clinical Finding 3, loss of brainstem reflexes; Clinical Finding 4, new-onset anisocoria; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; MRT, magnetic resonance tomography; PRES, posterior reversible leukoencephalopathy syndrome; v-a, venoarterial; v-v, venovenous.

[a]Acute condition leading to need for ECMO therapy.

[b]Additional condition which potentially leads to an intracerebral hemorrhage or ischemia by itself.

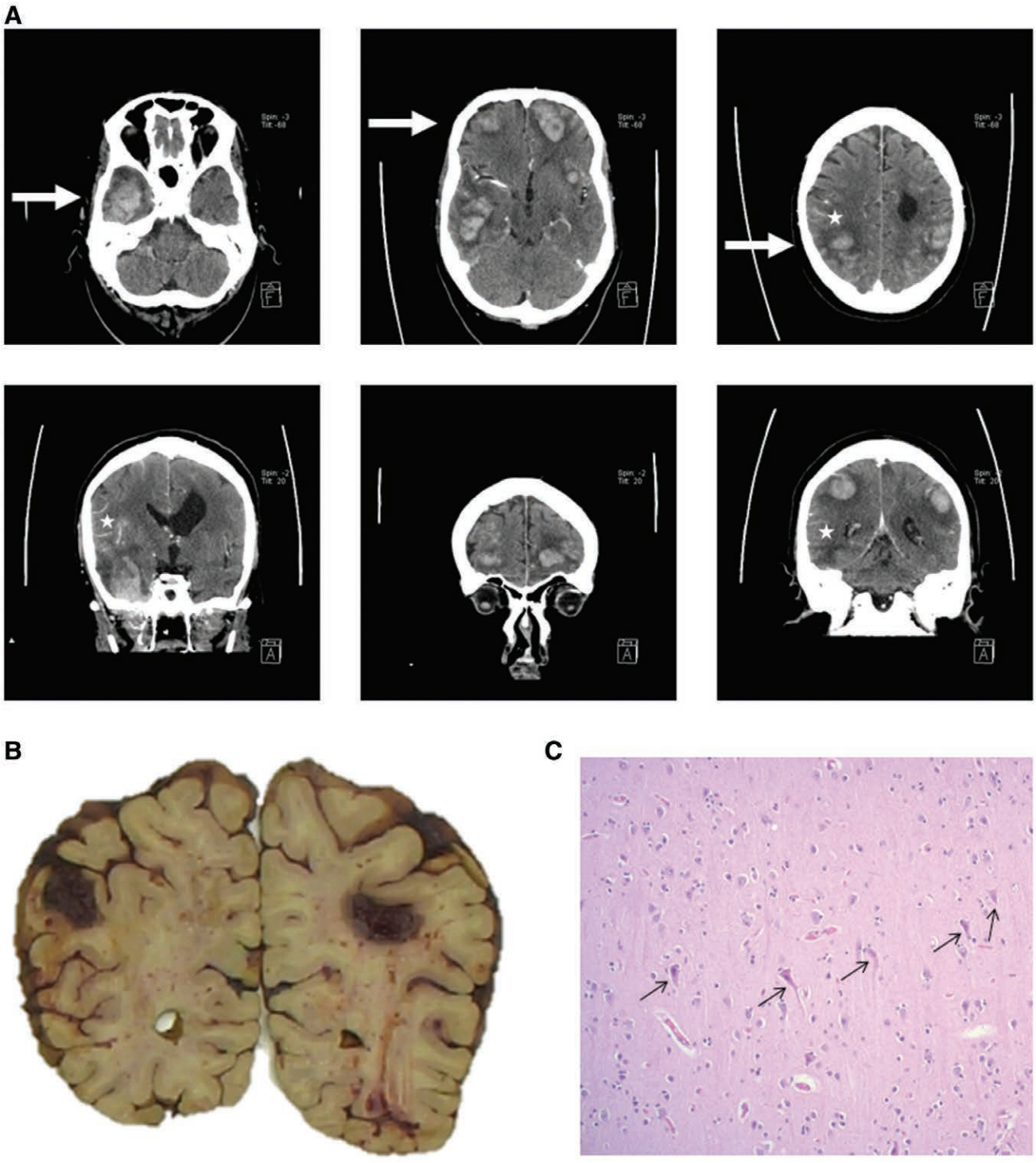

Figure. Male patient, 66 years old, with bilateral, primary viral pneumonia, who developed ARDS, which was treated with a v-v ECMO 3 days after admission to the ICU. A, Native cerebral CT scans at various axial (upper panel) and corresponding (white arrows in upper panel) coronal (lower panel) sections 9 days after ECMO installation showing multiple, massive intraparenchymal and subarachnoid hemorrhages (stars at exemplary locations). B, Coronal section of postmortem examination of the brain 30 days after admission revealing intracranial and subarachnoid hemorrhage accompanied by diffuse hypoxic-ischemic encephalopathy. C, Histologic preparations show "red neurons" (arrows) in the deeper layers of the cerebral cortex as evidence of acute neuronal injury. ARDS indicates acute respiratory distress syndrome; CT, computed tomography; ICU, intensive care unit; v-v ECMO, venovenous extracorporeal membrane oxygenation.

Regardless of the extent of hemorrhage, the treatment of ICH under ECMO support is especially challenging. Ongoing anticoagulation may worsen hemorrhage, while discontinuation may trigger thrombotic events. The surgical treatment of ICH remains controversial without proven benefit for patients under mechanical support in a 2014 case series.[10] However, the study largely involved patients with left ventricular assist devices (92%) and not ECMO (8%).[10]

Changes in coagulation and excessive anticoagulation are potential risk factors for ICH in ARDS patients treated on ECMO. To date, no widely accepted protocol exists for determining the optimal degree of anticoagulation with existing approaches to anticoagulation differ widely between ECMO centers.[8]

Although the precise onset of intracranial bleeding was unclear in our patients, we found no difference in anticoagulation or platelet counts between patients with or without neurologic injury. Our patient population had no evidence of vascular malformations or pathology as a potential risk factor for ICH. Bleeding was mainly localized to the supratentorial compartment, not clearly corresponding to a specific vascular territory or cannulation method. Data regarding this issue are sparse and inconsistent, with Risnes et al[3] reporting a higher frequency of late cerebral sequelae in v-a–cannulated patients. Intraparenchymal hemorrhage occurred spontaneously or as a secondary event in ischemic areas of the brain.

In conclusion, our report demonstrates that severe ICH is a devastating event linked to high mortality in patients undergoing ECMO for severe ARDS. To reduce the incidence of ICH in patients undergoing ECMO, more studies are needed to better define risk factors and the causes of ECMO-associated ICH, as well as to identify monitoring strategies to facilitate early diagnosis and optimal anticoagulation.

DISCLOSURES

Name: Stephanie Klinzing, MD.
Contribution: This author helped in conception of the work, design the study, collect, analyze, and interpret the data, and draft and approve the final manuscript.
Name: Urs Wenger, MD.
Contribution: This author helped collect and analyze the data and approve the final manuscript.
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Name: Urs Schwarz, MD.
Contribution: This author helped collect, analyze, and interpret the data and approve the final manuscript.
Name: Marco Maggiorini, MD.
Contribution: This author helped in conception of the work, design the study, analyze and interpret the data, and revise and approve the final manuscript.
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